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THE NATURE, MODES OF ACTION, AND TOXICITY OF RODENTICIDES

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INTRODUCTION

The previous edition of this chapter was published in 1981[1] with the intent to provide a broad review of the majority of chemicals that were currently used, or had been used at one time, as rodenticides. A major change in the present chapter has been the deletion of many rodenticides that are no longer in use because they were not economically feasible to develop; did not have the required specificity; were cumulative and/or persistent in the environment; and have been determined by regulatory agencies to have negative aspects in their use that are greater than the positive aspects.

Only the most widely known and used chemicals that were previously discussed in 1981,[1] as well as recent advancements with newer chemicals are reviewed here. The oral toxicity of some rodenticides are listed in Table 1.

ACUTE RODENTICIDES

Acute, single-dose toxicants are useful for rapid population reduction with mortalities usually occurring in less than 24 h, although with some of the newer chemicals, toxic symptoms may be delayed for several days. Most are nonspecific toxicants and must be applied carefully to avoid hazards to humans and nontarget animals. The characteristics of acute toxicants have been reviewed by Gratz[2] and Lund.[3] It is recommended that they not be used more often than twice a year because rodent populations may develop that will not accept the bait or toxicant, a condition known as "bait shyness".[4]

ZINC PHOSPHIDE

Zinc phosphide (Zn_3P_2), an inorganic chemical, is widely used and has a relatively good safety record to humans and wildlife. A nonspecific poison, it is used against a variety of rodents and can cause primary toxicity to rabbits and birds.[5] It was the first chemical to be registered in the U.S. for incrop use against rats that damage sugarcane.[6] The toxicity of zinc phosphide is caused by the highly toxic gas phosphine (PH_3) which forms when zinc phosphide reacts with water and hydrochloric acid in the gastrointestinal tract. Phosphine produces characteristic poisoning symptoms in the liver and lung. Secondary poisoning is usually not a problem with zinc phosphide,[5,7] but it has been reported in cats after they consumed rats that ate a bait containing 5% zinc phosphide.[8]

RED SQUILL

Red squill *(Urginea maritima)*, also known as the sea onion, is a plant belonging to the lily family that grows in the Mediterranean area. Powders and extracts of red squill have been used as rodenticides for hundreds of years.[8] Glycosides are the principle active ingredients, and one of them known as scilliroside, 6β-(acetyloxy)-3β-(β-D-glucopyranosyloxy)-8,14-dihydroxybufa-4,20,22-trienolide, has an acute oral LD_{50} of 0.7 mg/kg in male Norway rats and 0.43 mg/kg in females.[9] Red squill preparations can vary a great deal in toxicity, but two preparations have been developed that reduce this variability and increase the toxicity. The first, known as "fortification", increases the toxicity of weak preparations by combining them with an extract from red squill.[10] Normally it is standardized to an oral LD_{50} of 500 mg/kg in male Norway rats. The second is known as stabilized scilliroside and contains

TABLE 1
The Oral Toxicity[a] of Some Rodenticides

Common chemical name	Mouse	Rat	Cat	Dog	Pig	Chicken	Ref.
Zinc phosphide	C	C	C	C	C	C	6, 7, 16, 25, 86
Red squill	C	A, D, E	—	—	D	—	7, 16, 25, 86
Strychnine	B	C	A	B, C, D	D	—	7, 16, 25
1080 and 1081	A, B	A, B	A	A	A	B, C	7, 16, 25
Bromethalin	B	B	B	B			86
Calciferol	C	C	—	B	—	—	86, 89
Cholecalciferol	C	C	—	—	—	—	32
Warfarin	D	B, C, D (1 × 5)[b] (3.4 × 5)	B, C, D (3 × 5)	C, D (3 × 5)	B, C (0.4 × 5)	D, E (10 × 5)	16, 25, 51, 87, 88
Difenacoum	A (0.07 × 5)	B (0.18 × 5)	C, D	C	C	C	44, 86
Brodifacoum	A (0.04 × 5)	A (0.06—0.14 × 5)	C	B	A, B	C	45, 86
Bromadiolone	B	B	—	C	C	—	47, 86
Flocoumafen	A, B	A		A	C		66, 86
Difethialone	A	A	—	—	—	—	49
Diphacinone	—	B	C	B	D	—	32, 86, 90
Chlorophacinone	A, B	A, B	—	—	—	—	32
α-chlorohydrin	D	D	D	D	D	D[c]	82

[a] = Acute toxicity unless otherwise noted; toxic categories in mg/kg: A = 0.0—1.0; B = 1.1—10.0; C = 10.1—100; D = 101—1000; E = greater than 1001.
[b] = LD_{50} chronic toxicity, dose (mg/kg) × number of days administered.
[c] = For turkey.

0.5% scilliroside as the active ingredient.[11] Bait shyness develops quickly with red squill, but recent studies have provided detailed data about the glycosides which may lead to a product that is better accepted by rats.[12,13] For instance, scilliroside, which is bitter, can be enzymatically cleaved to scillirosidin, which is tasteless. The toxicity of scillirosidin is about the same as scilliroside. In rodents red squill produces death through central nervous system (CNS) convulsions. The selective rodenticidal properties of red squill are due in part to its ability to produce emesis in nontarget species such as the dog. Rats cannot vomit to get rid of the poison.

STRYCHNINE

Strychnine, strychnidin-10-one, an alkaloid obtained from the seeds of *Strychnos nux-vomica* and other *Strychnos* species, was discovered in 1817.[14] As early as 1640 these seeds were used in Europe as a poison.[8] Strychnine can be used as the alkaloid, but its salts such as sulfate can also be used. Strychnine is a potent convulsant and is rapidly absorbed from the gastrointestinal tract.[15] Convulsive seizures commonly appear within 5 to 30 min after ingestion, and the usual cause of death is respiratory failure. Strychnine is a nonspecific poison that is highly toxic to both mammals[16] and birds.[17] Acute oral LD_{50}s of less than 25 mg/kg are common, and for most animals the LD_{50} is less than 5 mg/kg.

Because of its high primary toxicity to nontarget wildlife, the placement of strychnine baits is important. Underground baiting for pocket gophers *(Geomys bursarius)* reduced its hazard to other animals,[18] but surface baiting can cause primary toxicity to small mammals and birds.[5]

Strychnine is rapidly detoxified and excreted and does not usually cause secondary poisoning. However, target species usually die quickly from strychnine, and they may contain strychnine bait in their gastrointestinal tracts or mouths which may be toxic to predators, such as mink *(Mustela vison)*, but not to raptors.[19]

SODIUM MONOFLUOROACETATE (SODIUM FLUOROACETATE; 1080)

Sodium fluoroacetate is a potent nonspecific toxicant with lethal doses commonly below 10 mg/kg in most mammals[16] and birds.[17]

Fluoroacetate is metabolized into the highly toxic chemical fluorocitrate. This process has been called "lethal synthesis" and signifies the conversion of an inactive chemical (fluoroacetate) into a lethal substance by tissue enzymes.[20] Fluorocitrate disrupts metabolism in the tricarboxylic acid (Krebs) cycle which is a major pathway for producing energy. Two different mechanisms of action of fluorocitrate have been described. In the first, aconitase, which is responsible for citrate metabolism, is inhibited.[21] The second mechanism involves inactivation of citrate transport in mitochondrial walls.[22,23] Whatever the actual mechanism, the end result of either is that cellular energy production is inhibited.

Fluoroacetate toxic symptoms may be delayed for several hours and depending on the species of animals may show a wide variation in response.[21] The heart and CNS are the major organs affected, and in herbivores cardiac effects predominate whereas in carnivores CNS depression and convulsions are the rule. In omnivores both cardiac and CNS symptoms are manifested. Respiratory or cardiac failure may be the cause of death. Fluoroacetate does not have an antidote. Primary and secondary poisoning can be a problem with sodium fluoroacetate.[5,7]

FLUOROACETAMIDE (1081)

Fluoroacetamide and sodium fluoroacetate are chemically similar. When fluoroacetamide is converted to fluoroacetate either through hydrolysis[21] or by action of the enzyme amidase,[24] its toxic manifestations resemble those of sodium fluoroacetate. Although fluoroacetamide is less toxic than sodium fluoroacetate in mammals,[25] and presumably birds, it is still

classified as a very toxic chemical. As compared to sodium fluoroacetate, fluoroacetamide has a slower onset of action.

CALCIFEROL (VITAMIN D_2)

Calciferol, 9,10-secoergosta-5,7,10(19),22-tetraen-3-ol, is a nonspecific toxicant with high cumulative effects and was introduced in 1973 for use against anticoagulant resistant mice and rats.[26,29] Calciferol was originally intended for use in combination with warfarin with the rationale that the development of resistance to either ingredient would be less because they had different modes of action.[30] Calciferol disrupts calcium metabolism and produces hypercalcemia by promoting the resorption of calcium from bones and the intestinal absorption of calcium. Calcium salts are deposited in soft tissues such as the kidneys, blood vessels, heart, and lungs.[31] Symptoms of toxicity such as anorexia, diarrhea, and thirst usually develop about 2 d after ingestion, but death can be delayed for as long as 7 d. There is no specific antidote to calciferol poisoning.

CHOLECALCIFEROL (VITAMIN D_3)

Cholecalciferol, 9,10-secocholesta-5,7,10(19)-trien-3-ol, was introduced in the early 1980s and is effective as a single- and multiple-feeding rodenticide.[32,33] Its mechanism of action and symptoms of toxicity are similar to calciferol, and it has low secondary hazards.

BROMETHALIN (EL-614)

Bromethalin, *N*-methyl-2,4-dinitro-*N*-(2,4,6-tribromophenyl)-6-(trifluoromethyl) benzenamine, was discovered in the late 1970s.[34] Its mechanism of action is in the CNS by uncoupling oxidative phosphorylation in the mitochondria which leads to decreased production of cellular energy, decreased cellular membrane transport, and increased pressure in cerebrospinal fluid.[35] Lethargy and paralysis preceding death in 2 to 3 d are common symptoms. It is highly toxic with LD_{50}s of 2 to 13 mg/kg for several species of animals and is effective against warfarin-resistant rats and mice.[36] Laboratory and field-baiting tests against rats and mice resulted in excellent bait acceptance, no bait shyness, and a high degree of efficacy (usually greater than 90% population reduction). Toxicological and field efficacy data for bromethalin have been summarized.[37]

FLUPROPADINE

Flupropadine, 1-(3,5-bistrifluoromethyl phenyl)-3-(4-tertbutyl piperidino)-prop-1-yne, is a new rodenticide that has shown good control of Norway rats and house mice in both laboratory and field tests.[38,39] Flupropadine is a chronic, cumulative toxicant when used in baits at concentrations of 0.1 to 0.2% with mortalities delayed 4 to 9 d following treatment. It is effective against warfarin-resistant rats.[40] No data have been published on its mechanism of action.

ANTICOAGULANT RODENTICIDES

There are two main chemical anticoagulant classes of rodenticides, the coumarins and the indandiones. These chemicals were introduced during the 1940s and 1950s and are still widely used. Anticoagulants have several rodenticidal properties that are distinct from the acute toxicants. First, toxic symptoms are delayed for several days, and rodents consume lethal doses before they stop feeding on baits. This property almost eliminates the problem of bait shyness which is common with acute toxicants. Second, the concentrations of anticoagulants in baits are low, and multiple doses (feedings) over several days are usually needed to produce death. Third, vitamin K_1 is an effective antidote to toxic symptoms produced by the anticoagulants. Coumarin and indandiones are nonspecific and are effective

against a wide range of rodents. Several anticoagulants have recently been reviewed by Lund.[41]

COUMARINS

Development of the coumarin derivatives goes back to the 1920s when the "sweet clover disease" that causes bleeding in cattle was described. The chemical responsible for the hemorrhaging was identified as 3,3-methylenebis(4-hydroxy-2H-1-benzopyran-2-one), which is better known as dicumarol and is used in human medicine.[31] Successful field trials were conducted with dicumarol, but warfarin, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one, was found to be more effective.[42] In addition to dicumarol and warfarin, three other coumarins that have been used extensively as rodenticides are coumafuryl, 3-[1-(2-furanyl)-3-oxobutyl]-4-hydroxy-2H-1-benzopyran-2-one; coumachlor, 3-[1-(4-chlorophenyl)-3-oxobutyl]-4-hydroxy-2H-1-benzopyran-2-one; and coumatetralyl,4-hydroxy-3-(1,2,3,4-tetrahydronaphthalemyl)-2H-1-benzopyran-2-one.[43] The latter chemicals are known as the first-generation anticoagulants, but rodent resistance (warfarin anticoagulant resistance) to them has developed. The development of anticoagulant resistance was the stimulus for the introduction of difenacoum,[44] 3-[3-(1,1'-biphenyl)-4-yl-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzopyran-2-one; brodifacoum,[45] 3-[3-(4'-bromo-1-1'-biphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthalenly]-4-hydroxy-2H-1-benzopyran-2-one; and bromadiolone,[46-47] 3-[3-(4'-bromo(1,1'-biphenyl)-4-yl]-3-hydroxy-1-phenylpropyl]-4-hydroxy-2H-1-benzopyran-2-one. These chemicals are coumarin derivatives known as second-generation anticoagulants and generally are effective against warfarin resistant rodents. More recently, two additional second-generation anti-coagulants effective against resistant rodents have been developed: flocoumafen,[48] 4-hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl] coumarin, and difethialone,[49] 3-[4-bromo(1,1-biphenyl)-4-yl]-1,2,3,4-tetrahydro-1-naphthalenyl-4-hydroxy-benzothiopyran-2-one. In difethialone, the oxygen in the 1-hydroxy-4-coumarin has been replaced by sulfur and represents a new anticoagulant chemical class called hydroxy-4-benzothiopyranones. The second-generation anticoagulants have the same mechanism of action and antidotal procedures as the other coumarins, but they will be discussed separately because they have rodenticidal properties that are unique from the others.

Since the effects of coumarin and indandione derivatives as rodenticides are qualitatively similar, comments on the pharmacology of warfarin will serve as an example for all oral anticoagulants.[31] Warfarin functions as an antivitamin which reversibly competes with vitamin K in the liver. Vitamin K is essential for the synthesis of blood clotting factors in the liver known as II (prothrombin), VII, IX, and X. Oral anticoagulants depress the formation of these factors, and prothrombin, which is converted into thrombin by the action of the other three, is not available to act on fibrinogen to form the fibrin clot in the blood. Toxic manifestations after ingestion of oral anticoagulants are delayed for several days because clotting factors circulate in the blood, and time is required for their natural disappearance. Death is caused by hemorrhaging. Vitamin K_1 is a specific antidote, but blood transfusions may be necessary if hemorrhaging is severe.

Primary poisoning from the use of warfarin baits has been documented in the deaths of dogs, cats, and hogs[50,51] and although field data are lacking, other anticoagulants have the potential to kill nontarget species also.

Attempts have been made to increase the effectiveness of warfarin by combining it with the antibiotic sulfaquinoxaline. The rationale is that sulfaquinoxaline kills intestinal bacteria that produce vitamin K. With less vitamin K available anticoagulants should be more effective. Sulfaquinoxaline was effective in one study[52] but not in another.[53] However, a significant control of house mice was reported when sulfaquinoxaline was added to warfarin tracking powder.[54]

Secondary poisoning from anticoagulants appears to be low, but the data are limited,

especially from field studies. Laboratory studies have shown that nutria *(Myocaster coypus)* killed with warfarin were lethal to dogs and mink, but rodents killed with warfarin did not pose a hazard to tawny owls.[55] In another study, mortality was observed in owls fed bromadiolone-, brodifacoum-, or diphacinone-killed rats.[55] In one field study,[57] consumption of brodifacoum-killed voles were implicated as causing secondary poisoning to screech owls.

In general, the first-generation anticoagulants require multiple feedings and are about equally effective. With warfarin in the forefront, they were the primary method of rodent control in the 1950s. However, resistance to warfarin was discovered in wild Norway rats and mice, and there is also cross resistance to the other coumarins and the indandiones. In studies with anticoagulant resistant rats, coumatetralyl was found to be more effective than warfarin.[58,59] This observation suggested that chemical modifications on the side chain moiety of the 4-hydroxycoumarin might yield chemicals effective in resistant rats.[60] Subsequently, the second-generation anticoagulants were evaluated and found to have three remarkable properties as oral anticoagulants;[49-49] they are (1) highly potent with LD_{50}s of less than 5 mg/kg in several target rodent species; (2) highly effective after a single feeding; and (3) effective against warfarin-resistant rats.

Difenacoum[44,61] produces effective control in several species including house mice, wild Norway, ricefield *(R. r. mindanensis)*, Polynesian *(R. exulans)*, Nile *(Arvicanthis niloticus)*, lesser bandicoot *(Bandicota bengalensis)*, and short-tailed bandicoot *(Nesokia indica)* rats, and the Indian gerbil *(Tatera indica)*. The primary toxicity of difenacoum baits offers a margin of safety that is equal to or larger than warfarin to such domestic species as the cat, dog, and pig.[44]

Brodifacoum is the brominated derivative of difenacoum, and it is more toxic to rats and mice than is difenacoum.[62] The efficacy and toxicity of brodifacoum have been reviewed by Kaukeinen and Rampaud.[63]

Bromadiolone is also effective against a wide variety of pest species including the roof rat, pocket gopher *(Thomomys bottae)*, ground squirrel *(Spermophilus beecheyi)*, and African white-tailed rat *(Mystromys albicaudatus)*.[45] Toxicology, secondary hazard, and efficacy data have been summarized for bromadiolone.[64]

Although the initial data showed that difenacoum, brodifacoum, and bromadiolone were effective against warfarin-resistant rats and mice, recent reports indicate that there is resistance to difenacoum and bromadiolone, and a higher tolerance to brodifacoum.[65]

The acute oral LD_{50} of flocoumafen to several rodent species ranges from 0.25 to 4.2 mg/kg with mortalities in about 3 to 10 d after treatment.[66] Field tests against house mice have been successful,[67] and field trials in the Philippines resulted in excellent rat control with no appreciable effects observed in nontarget animals.[68]

Difethialone is also a potent toxicant.[49] Acute oral LD_{50}s for wild Norway rats, roof rats, and house mice are 0.51, 0.38, and 0.47 mg/kg, respectively. It is effective against warfarin-resistant rats and mice with death times ranging from about 3 to 10 d.

INDANDIONES

In addition to their anticoagulant properties[69] which were discovered in 1944, some indandiones have insecticidal properties.[70] The commonly used indandione rodenticides are pindone, 2-(2,2-dimethyl-1-oxo-propyl)-1H-indene-1,3(2H)-dione; diphacinone, 2-(diphenylacetyl)-1H-indene-1,3(2H)-dione; and chlorophacinone, 2-[(4-chlorophenyl)phenylacetyl]-1H-indene-1,3(2H)-dione.[43] Like the coumarins, the toxicity of small multiple doses of indandiones is caused by disruption of blood coagulation mechanisms, but unlike the coumarins, large single doses of indandiones are lethal in 2 to 12 h without appreciable effects on blood clotting.[69] Labored breathing, muscular weakness, pulmonary congestion, venous engorgement, and hyperexcitability are toxic signs after large single doses of indandiones. These symptoms of toxicity are not seen in rodenticide applications.

Nutria killed with diphacinone, pindone, and the calcium salt of 2-isovaleryl-1,3-indandione caused death when fed to dogs and mink,[71] but the significance of this finding under field conditions is not known. In addition to its rodenticidal properties, diphacinone is also used to control vampire bats[72] *(Desmodus rotundus)*.

FUMIGANTS

Fumigants are nonspecific acute toxicants that are effective by inhalation. They are widely used as insecticides and when used for that purpose, they can also kill rodents. Fumigants are not as economical as poisonous baits,[73] but they can be used when baits are ineffective, impractical, or hazardous to use. Fumigants are employed in closed situations such as burrows, ships, and warehouses, and with these types of applications they are very specific for the target rodents. Secondary poisoning from the use of fumigants is nil. The uses, applications, and properties of several fumigants have been previously described.[74,75] There has not been widespread use of fumigants for controlling rodents. Calcium cyanide, sodium cyanide, carbon bisulfide, methyl bromide, aluminum phosphide, and chloropicrin have been reviewed[1] and will not be discussed again in this section.

A formulation of two ingredients, 65% sodium nitrate and 35% charcoal, is an effective gas cartridge for burrowing rodents[76-78] and coyote dens.[76] When these two ingredients are ignited, large amounts of carbon monoxide are produced. Another gas cartridge consisting of 55% potassium nitrate and 45% sawdust was also found to be effective against several rodents.[79]

CHEMOSTERILANTS

Chemosterilants (antifertility agents) are reproductive inhibitors that may interfere with the reproductive cycle at many different stages in either male or females, juveniles or adults. Their use in rodent control has remained largely academic because these agents have a combination of factors such as palatability, nonspecificity, and short residual biological activity that make them impractical.[80] An extensive review has been made on 22 chemicals,[81] but only 2 have apparently ever achieved any practical significance as chemosterilants. The two chemicals are 3-chloro-1,2-propanediol (also known as α-chlorohydrin and U-5897) and butandiol-*bis*-methane sulfonic acid ester.

α-Chlorohydrin, classified as a toxicant-sterilant,[82] is a male chemosterilant that produces epididymal lesions which block passage of sperm.[83] In albino rats reversible sterility is produced with low doses whereas high doses (45 mg/kg) produced permanent sterility. Laboratory tests with U-5897 in ricefield *(R. argentiventer)* and Polynesian rats did not produce lesions with doses as high as 300 mg/kg.[84] A unique feature of α-chlorohydrin is that low doses produce sterility in susceptible species and higher doses produce mortality. It has produced good field results in several rodent species.[82]

Butandiol-*bis*-methane sulfonic acid ester is an alkylating agent which prevents development of the testes or ovaries in young rats.[85] Its LD_{50} in rats is 30 mg/kg, and it has been suggested that it acts as a lethal agent since there was minimal rat activity 3 weeks after application. Mortality occurs in both males and females when large amounts are consumed, and it can be classified as a sterilant-toxicant. No recent references were available.

REFERENCES

1. **Savarie, P. J.,** The nature, modes of action, and toxicity of rodenticides, in *Handbook of Pest Management in Agriculture*, Vol. 3, Pimentel, D., Ed., CRC Press, Boca Raton, FL, 1981, 113.
2. **Gratz, N. G.,** A critical review of currently used single-dose rodenticides, *Bull. W.H.O.*, 48, 469, 1973.
3. **Lund, M.,** Nonanticoagulant rodenticides, in *Rodent Pest Management*, Prakash, I., Ed., CRC Press, Boca Raton, FL, 1988, chap. 19.
4. **Howard, W. E. and Marsh, R. E.,** Rat control manual, *Pest Control*, 42, D, 1974.
5. **Colvin, B. A., Hegdal, P. L., and Jackson, W. B.,** Review of non-target hazards associated with rodenticide use in the USA, *OEPP/EPPO BULL.*, 18, 301, 1988.
6. **Hood, G. A.,** Zinc phosphide—A new look at an old rodenticide for field rodents, *Proc. Vertebr. Pest Conf.*, 5, 85, 1972.
7. **Rudd, R. L. and Genelly, R. E.,** Pesticides: their use and toxicity in relation to wildlife, *Calif. Dep. Fish Game, Fish Bull.* No. 7, 1956.
8. **Chitty, D. and Southern, H. N.,** *Control of Rats and Mice*, Vol. 1, 2, and 3, Oxford Univ. Press, London, 1954.
9. **Stoll, A. and Renz, J.,** Uber Scillirosid, ein gegen Nager spezifisch wirksames Gift der roten Meerzwiebel, *Helv. Chim. Acta*, 25, 43, 1942.
10. **Crabtree, D. G., Ward, J. C., and Garlough, F. E.,** The fortification of red quill *(Urginea maritima)* by means of an extract of red squill, *J. Am. Pharm. Assoc.*, 31, 142, 1942.
11. **Maddock, R. R. and Schoof, H. F.,** New red squill derivative: laboratory and field studies on stabilized scilliroside against Norway rats, *Pest Control*, 38, 45, 1970.
12. **Verbiscar, A. J., Banigan, T. F., and Gentry, H. C.,** Recent research on red squill as a rodenticide, *Proc. Vertebr. Pest Conf.*, 12, 51, 1986.
13. **Verbiscar, A. J., Banigan, T. F., and Schotz, R. A.,** Modification of red squill by *Aspergillus niger*, *J. Agric. Food Chem.*, 35, 365, 1987.
14. **Henry, T. A.,** *The Plant Alkaloids*, J. and A. Churchill, London, 1913.
15. **Gleason, M. N., Gosselin, R. E., Hodge, H. C., and Smith, R. P.,** *Clinical Toxicology of Commercial Products*, Section III, Williams & Wilkins Co., Baltimore, 1969.
16. **Spector, W. S., Ed.,** *Handbook of Toxicology. Vol. I. Acute Toxicicities of Solids, Liquids, and Gases to Laboratory Animals*, W. B. Saunders, Philadelphia, 1956.
17. **Hudson, R. H., Tucker, R. K., and Haegele, M. A.,** *Handbook of Toxicity of Pesticides to Wildlife*, 2nd ed., Publ. No. 153, Fish and Wildlife Service, U.S. Department of Interior, Washington, D.C., 1984.
18. **Hegdal, P. L. and Gatz, T. A.,** Hazards to wildlife associated with underground strychnine baiting for pocket gophers, *Proc. Vertebr. Pest Conf.*, 7, 258, 1976.
19. **Anthony, R. M., Lindsey, G. D., and Evans, J.,** Hazards to golden-mantled ground squirrels and associated secondary hazard potential from strychnine for forest pocket gophers, *Proc. Vertebr. Pest Conf.*, 11, 15, 1984.
20. **Peter, R. A.,** Lethal synthesis (Croonian lecture), *Proc. R. Soc. London, Ser. B*, 139, 143, 1952.
21. **Pattison, F. L. M.,** *Toxic Aliphatic Fluorine Compounds*, Elsevier, New York, 1959.
22. **Kun, E., Kirsten, E., and Sharma, M. L.,** Enzymatic formation of glutathione-citryl thioester by a mitochondrial system and its inhibition by (−) erythrofluorocitrate, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 4942, 1977.
23. **Kirsten, E., Sharma, M. L., and Kun, E.,** Molecular toxicology of (−) erythro-fluorocitrate: selection inhibition of citrate transport in mitochondria and the binding of fluorocitrate to mitochondrial proteins, *Mol. Pharmacol.*, 14, 172, 1978.
24. **Matsumura, F. and O'Brien, R. D.,** A comparative study of the modes of action of fluoroacetamide and fluoroacetate in the mouse and American cockroach, *Biochem. Pharmacol.*, 12, 1201, 1963.
25. **Fairchild, E. J., Ed.,** *Agricultural Chemicals and Pesticides*, U.S. Department of Health Education and Welfare, DHEW (NIOSH) Publication No. 71-180, Cincinnati, Ohio, 1977.
26. **Meehan, A. P.,** A new rodenticide for warfarin-resistant mice, *Chem. Drug.*, 209, 20, 1978.
27. **Rennison, B. D.,** Field trials of calciferol against warfarin resistant infestations of the Norway rat (*Rattus norvegicus* Berk.), *J. Hyg., Camb.*, 73, 353, 1974.
28. **Rowe, F. P., Smith, F. J., and Swinney, T.,** Field trials of calciferol combined with warfarin against wild house-mice (*Mus musculus* L.), *J. Hyg., Camb.*, 73, 353, 1974.
29. **Greaves, J. H., Redfern, R., and King, R. E.,** Some properties of calciferol as a rodenticide, *J. Hyg., Camb.*, 73, 341, 1974.
30. Pest Infestation Control laboratory, A New Rodenticide, Tech. Circ. No. 30, Ministry of Agriculture, Fisheries and Food, Surrey, England, November 1973.
31. **Gilman, A. G., Goodman, L. S., Rall, T. W., and Murad, F., Eds.,** *The Pharmacological Basis of Therapeutics*, 7th ed., Macmillan, New York, 1985.

32. **Marshall, E. F.**, Cholecalciferol: a unique toxicant for rodent control, *Proc. Vertebr. Pest Conf.*, 11, 95, 1984.
33. **Brown, L. D. and Marshal, E. F.**, Field evaluation of Quintox (cholecalciferol) for controlling commensal rodents, *Proc. Vertebr. Pest Conf.*, 13, 70, 1988.
34. **Drekorn, B. A., O'Doherty, G. O. P., Clinton, A. J., and Kramer, K. E.**, EL-614, a novel acute rodenticide, *Proc. Br. Crop Prot. Conf.*, 491, 1979.
35. **Van Lier, R. B. L. and Ottosen, L. D.**, Studies on the mechanism of toxicity of bromethalin, a new rodenticide, *The Toxicol.*, 1, 114, 1981.
36. **Jackson, W. B.**, Bromethalin—A promising new rodenticide, *Proc. Vertebr. Pest Conf.*, 10, 10, 1982.
37. **Spaulding, S. R. and Spannring, H.**, Status of bromethalin outside the United States, *Proc. Vertebr. Pest Conf.*, 13, 64, 1988.
38. **Buckle, A. P.**, Field trials of a new sub-acute rodenticide flupropadine, against wild Norway rats *(Rattus norvegicus)*, *J. Hyg., Camb.*, 95, 505, 1985.
39. **Rowe, F. P., Bradfield, A., and Swinney, T.**, Pen and field trials of flupropadine against the house mouse (*Mus musculus* L.), *J. Hyg., Camb.*, 95, 513, 1985.
40. **Morgan, R. L. and Parnell, E. W.**, Flupropadine—a new rodenticide, *Br. Crop Prot. Counc.*, 37, 125, 1987.
41. **Lund, M.**, Anticoagulant rodenticides, in *Rodent Pest Management*, Prakash, I., Ed., CRC Press, Boca Raton, FL, 1988, chap. 20.
42. **Crabtree, D. G.**, Raticidal potentialities of WARF-42, *Soap Sanit. Chem.*, 26, 131, 1950.
43. **Bentley, E. W.**, A review of anticoagulant rodenticides in current use, *Bull. W.H.O.*, 47, 275, 1972.
44. **Bull, J. O.**, Laboratory and field investigations with Difenacoum, a promising new rodenticide, *Proc. Vertebr. Pest Conf.*, 7, 72, 1976.
45. **Dubock, A. C. and Kaukeinen, D. E.**, Brodifacoum (Talon® rodenticide), a novel concept, *Proc. Vertebr. Pest Conf.*, 8, 127, 1978.
46. **Marsh, R. E.**, Bromadiolone, a new anticoagulant rodenticide, *EPPO Bull.*, 7, 495, 1977.
47. **Meehan, A. P.**, Rodenticidal activity of Bromadiolone—a new anticoagulant, *Proc. Vertebr. Pest Conf.*, 8, 122, 1978.
48. **Rowe, F. P., Bradfield, A., and Seinney, T.**, Pen and field trials of a new anticoagulant rodenticide flocoumafen against the house mouse (*Mus musculus* L.), *J. Hyg., Camb.*, 95, 623, 1985.
49. **Lechevin, J. C. and Poche, R. M.**, Activity of LM2219 (Difethialone), a new anticoagulant rodenticide, in commensal rodents, *Proc. Verteor. Pest Conf.*, 13, 59, 1988.
50. **Papworth, D. C.**, A review of the dangers of warfarin poisoning to animals other than rodents, *R. Soc. Health J.*, 78, 52, 1958.
51. **Ashworth, B.**, The frequency of animal poisoning by warfarin, *Vet. Rec.*, 93, 50, 1973.
52. **Derse, P.**, Anti-K factor in anticoagulant rodenticides, Part II, *Soap Cosmet. Chem. Spec.*, 39, 84, 86, 1963.
53. **Drummond, D.**, Rats resistant to warfarin, *New Sci.*, 30, 771, 1966.
54. **Marsh, R. E. and Howard, W. E.**, New perspectives in rodent and mammal control, *Int. Biodeg. Symp.*, 3, 317, 1975.
55. **Townsend, M. G., Fletcher, M. R., Odam, E. M., and Stanley, P. I.**, An assessment of the secondary poisoning hazard of warfarin to tawny owls, *J. Wildl. Manage.*, 45, 243, 1981.
56. **Mendenhall, V. M. and Pank, L. F.**, Secondary poisoning of owls by anticoagulant rodenticides, *Wildl. Soc. Bull.*, 8, 311, 1980.
57. **Hegdal, P. L. and Colvin, B. A.**, Potential hazard to eastern screech-owls and other raptors of brodifacoum bait used for vole control in orchards, *Environ. Toxicol. Chem.*, 7, 245, 1988.
58. **Greaves, J. H. and Ayres, P.**, Some rodenticidal properties of coumatetralyl, *J. Hyg., Camb.*, 67, 311, 1969.
59. **Lund, M.**, Rodent resistance to the anticoagulant rodenticides, with particular reference to Denmark, *Bull. W.H.O.*, 47, 611, 1972.
60. **Hadler, M. R. and Shadbolt, R. S.**, Novel 4-hydroxycoumarin anticoagulants active against resistant rats, *Nature (London)*, 253, 275, 1975.
61. **Greaves, J. H. and Rehman, A. B.**, The susceptibility of *Tatera indica*, *Nesokia indica* and *Bandicota bengalensis* to three anticoagulant rodenticides, *J. Hyg., Camb.*, 78, 75, 1977.
62. **Redfern, R. and Gill, J. E.**, Laboratory evaluation of WBA 8119 as a rodenticide for use against warfarin-resistant and non-resistant rats and mice, *J. Hyg., Camb.*, 77, 419, 1976.
63. **Kaukeinen, D. E. and Rampaud, M.**, A review of brodifacoum efficacy in the U.S. and worldwide, *Proc. Vertebr. Pest Conf.*, 12, 16, 1986.
64. **Poche, R. M.**, The status of bromadiolone in the United States, *Proc. Vertebr. Pest Conf.*, 12, 6, 1986.
65. **Lund, M.**, Resistance to the second-generation anticoagulant rodenticides, *Proc. Vertebr. Pest Conf.*, 11, 89, 1984.

66. Lund, M., Flocoumafen—a new anticoagulant rodenticide, *Proc. Vertebr. Pest Conf.*, 13, 53, 1988.
67. Rowe, F. P., Bradfield, A., and Swinney, T., Pen and field trials of a new anticoagulant rodenticide flocoumafen against the house mouse (*Mus musculus* L.), *J. Hyg., Camb.*, 95, 623, 1985.
68. Hoque, M. M. and Olvida, J. L., Efficacy and environmental impact of flocoumafen (STORM) wax block baits used for ricefield rat control in the Phillippines, *Proc. Vertebr. Pest Conf.*, 13:75, 1988.
69. Kabat, H., Stohlman, E. F., and Smith, M. I., Hypoprothombinemia induced by administration of indandione derivations, *J. Pharmacol. Exp. Ther.*, 80, 160, 1944.
70. Kilgore, L. B., Ford, J. H., and Wolfe, W. C., Insecticidal properties of 1,3-indandiones, *Ind. Eng. Chem.*, 34, 494, 1942.
71. Evan, J. and Ward, A. L., Secondary poisoning associated with anticoagulant-killed Nutria, *J. Am. Vet. Med. Assoc.*, 151, 856, 1967.
72. Thompson, R. D., Mitchell, G. C., and Burns, R. J., Vampire bat control by systemic treatment of livestock with an anticoagulant, *Science*, 177, 806, 1972.
73. Miller, M. A., Poison gas tests on gophers, *Calif. Agric.*, 8, 7, 14, 1954.
74. Mallis, A., *Handbook of Pest Control*, 5th ed., MacNair Dorland Co., New York, 1969.
75. Torkelson, T. R., Hoyle, H. H., and Rowe, V. K., Toxicological hazards and properties of commonly used space, structural and certain other fumigants, *Pest Control*, 7, 13, 1966.
76. Savarie, P. J., Tigner, J. R., Elias, D. J., and Hayes, D. J., Development of a simple two-ingredient pyrotechnic fumigant, *Proc. Vertebr. Pest Conf.*, 9, 215, 1980.
77. Fagerstone, K., Matschke, G., and Elias, D., Radiotelemetry to evaluate effectiveness of a new fumigant cartridge for controlling ground squirrels, *Proc. 3rd Int. Conf. Wildl. Biotelemetry*, Laramie, WY, 20, 1981.
78. Matschke, G. H. and Fagerstone, K. A., Efficacy of a two-ingredient fumigant on Richardson's ground squirrels, *Proc. Vertebr. Pest Conf.*, 11, 17, 1984.
79. Zhi, D. and Chang, Z. W., Efficacy of a carbon monoxide gas cartridge against field rodents, *Proc. Vertebr. Pest Conf.*, 12, 163, 1986.
80. Marsh, R. E. and Howard, W. E., Prospects of chemosterilant and genetic control of rodents, *Bull. W.H.O.*, 48, 309, 1973.
81. Marsh, R. E., Chemosterilants for rodent control, in *Rodent Pest Management*, Prakash, I., Ed., CRC Press, Boca Raton, FL, 1988, chap. 21.
82. Ericsson, R. J., Alpha-chlorohydrin (EPIBLOC®): a toxicant-sterilant as an alternative in rodent control, *Proc. Vertebr. Pest Conf.*, 10, 6, 1982.
83. Ericsson, R. J., Male antifertility compound: U-5897 as a rat chemosterilant, *J. Reprod. Fertil.*, 22, 213, 1970.
84. Kennelly, J. J., Garrison, M. V., and Johns, B. E., Laboratory studies of the effect of U-5897 on the reproduction of wild male rats, *J. Wildl. Manage.*, 34, 508, 1970.
85. Lund, M., New rodenticides against anticoagulant-resistant rats and mice, *EPPO Bull.*, 7, 503, 1977.
86. Worthing, C. R. and Walker, S. B., *Pesticide Manual*, 8th ed., British Crop Protection Council, Thornton Health, U.K., 1987.
87. Steiniger, F., Uber die Wirksamkeit des 'Fumarin' eines neuen Antikoagulans zur Rattenbekampfung, und seine Vertraglichkeit fur Haustiere, *Nachrichtenbl. Dtsch. Pflanzenschutzdienstes, (Brauhschweig)*, 5, 167, 1953.
88. Hagan, E. C. and Radomski, J. L., The toxicity of 3-(acetonylbenzyl)-4-hydroxycoumarin (Warfarin) to laboratory animals, *J. Am. Phar. Assoc.*, 42, 379, 1953.
89. Sweet, D. V., Ed., Registry of toxic effects of chemical substances, 1985-86 ed., U.S. Department of Health and Human Services, Washington, D.C. 20402, 1987.
90. Gaines, T. B., Acute toxicity of pesticides, *Toxicol. Appl. Pharmacol.*, 14, 515, 1969.